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FOUNDED BY JOHN D. ROCKEFELLER

RETROGRADE DEGENERATION IN THE SPINAL NERVES

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE

OGDEN GRADUATE SCHOOL OF SCIENCE

IN CANDIDACY FOR THE

DEGREE OF

DOCTOR OF PHILOSOPHY

(DEPARTMENT OF NEUROLOGY)

BY

S. WALTER RANSON

CHICAGO

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RETROGRADE DEGENERATION IN THE SPINAL NERVES.

BY

S. WALTER RANSON.

(*From the Neurological Laboratory of the University of Chicago and the Anatomical Laboratory of the St. Louis University.*)[1]

1. *Summary of the Literature.*

Retrograde degeneration, sometimes also spoken of as "ascending degeneration" (FLEMING '97) and "indirect Wallerian degeneration" (VAN GEHUCHTEN '03), is a process resulting in the destruction of that portion of a divided fiber which is still connected with its cell of origin. Such cellulipetal changes are not in accord with the law of WALLER, which requires that of a divided nerve fiber only the portion severed from its trophic center should disintegrate, while all the rest of the neurone remains intact; nevertheless, this retrograde degeneration has been observed by a large number of investigators; it has been found in the cerebral as well as in the spinal nerves and occurs under certain conditions in various fiber tracts of the central system.

The investigations, which lead to the discovery of this form of degeneration, were carried out in the first instance upon the nerves in the central stumps of amputated limbs and upon the associated segments of the spinal cord. Experimental amputation and nerve resection in animals have served to confirm the observations made on human material and to eliminate complications introduced by the cause of the amputation or by the terminal disease. Since the cellulipetal changes resulting from the section of the spinal nerves are typical of retrograde degeneration, it has not seemed desirable to complicate matters by a review of the literature on similar changes in the cerebral nerves, nor in the fiber tracts of the central system. The observations along these lines have been

[1]While at the St. Louis University the writer received very valuable assistance, both in the operations and the enumerations, from Dr. FRED. B. WHITTIKER, to whom he is especially indebted.

very well analyzed by VAN GEHUCHTEN ('03) and briefly summarized by the present writer ('04). It is also believed that we may omit without loss any mention of the theories of the different investigators concerning the nature and cause of the cellulipetal alterations resulting from the section of nerves.

In studying the literature on retrograde degeneration in the spinal nerves, it was found convenient to arrange the results of the different investigators in tabular form, placing the changes found in the various parts of the nervous system in separate columns under the following headings: central stumps of the severed nerves, ventral roots, dorsal roots, spinal ganglia, the spinal cord in general, the ventral horns and motor cells, the dorsal horns and the dorsal funiculi. In this way were tabulated the changes found in sixty-nine autopsies upon cases of more or less long standing amputation. In a separate table of the same kind were summarized the changes observed by eighteen different investigators who had carried out experimental amputation and nerve resection in animals. When these tables were completed, it was possible to compare the results of the different investigators and see what changes were constant in any part of the nervous system. It is with reference to these tables that the following has been written, and for this reason it has been possible to make accurate, but at the same time very general, statements.

The first observation of an alteration propagated centrally along the course of an injured nerve was made in 1829 by BERARD, who noticed that the ventral roots, associated with the nerves of an amputated limb, were smaller than their fellows on the opposite side. But it was not until 1868-69 that VULPIAN and DICKINSON aroused general interest in the subject, an interest which has led to an almost uninterrupted series of investigations and even at the present time has not abated. The results of this series of investigations may be stated rather briefly.

In a considerable proportion of the cases, no notice was taken of the central stumps of the severed nerves. Of those who did include these structures in their investigations only two found them normal (FRIEDREICH '73, and DRESCHFELD '79). The complete degeneration, seen in one of DICKINSON's ('68) cases, was undoubtedly due to extraneous causes, probably septic infection. In all the other cases of amputation a simple atrophy, associated with a marked decrease in the average diameter of the nerve fibers, pre-

sents itself with striking uniformity (VULPIAN '68-'69, ERLENMEYER '72, HAYEM '76, DÉJERINE and MAYOR '78, HAYEM and GILBERT '84, FRIEDLÄNDER and KRAUSE '86, DUDLEY '86, REYNOLDS '87, MARINESCO '92, ELZHOLZ '00, on human material; and HOMÉN '90, VANLAIR '91, PILCZ '99, on animals). The microscopical changes are of some importance. The individual fibers are much decreased in size, the change affecting chiefly the myelin sheaths. Many of the fibers are entirely devoid of myelin and there is a tendency for them to be grouped in bundles. These altered fibers have been interpreted, sometimes as atrophied, sometimes as regenerated fibers; but the former interpretation seems to be the better supported. Of the authors who have placed themselves on record with regard to this point, six regard the change as an atrophy, while four believe that the altered fibers represent an attempt at regeneration; and on the side of the majority are included the two most thorough investigations: that of FRIEDLÄNDER and KRAUSE ('86) recording eight cases of amputation, and that of HOMÉN ('90) recording experiments on more than forty dogs.

As a typical account of these alterations we may summarize the description given by FRIEDLÄNDER and KRAUSE ('86). In their eight cases the nerve stumps presented patches of normal appearance separated by areas entirely devoid of medullated fibers; still other areas, constituting the larger portion of the cross-section contained about half the proper number. In the atrophied bundles the individual fibers are about one-third their normal size, and may be recognized as faint refractile rings, which do not take the WEIGERT stain. At the center of these rings a barely recognizable point represents the remains of the axis cylinder.

In addition to this simple atrophy there occurs in the proximal portion of some of the severed nerve fibers a true degeneration, not distinguishable histologically from Wallerian degeneration. This may be seen in MARCHI preparations from the central stumps of experimentally resected nerves, removed twenty to forty days after the operation (REDLICK '93, MOSCHAEW '93, BIEDL '97). Some observers have reported negative results with this stain; but it must be remembered in this connection that the degeneration in the central stump occurs about fifteen days later than true Wallerian degeneration (BIEDL '97, VAN GEHUCHTEN '03), and that the peripheral degeneration is at its height at a time when the

alterations in the central stump are just beginning. Too early an examination of the material may thus lead to erroneous conclusions.

The changes in the ventral root are less marked than in the mixed nerve, and until the last twenty years these structures were often reported normal (Vulpian '68-'69, Dickinson '68, Déjerine and Mayor '78, Dreschfeld '79, Friedländer and Krause '86). Atrophy of the ventral roots was reported by Bérard ('29), Türck ('53), Genzmer ('76), Hayem and Gilbert ('84), and Edinger ('88); and during the last two decades has been quite uniformly observed (Kahler and Pick '80, Reynolds '87, Marinesco '92 and Wille '95). According to Reynolds the atrophy is due to an increase in the proportion of the small fibers, while in two of Wille's cases it was due to a decrease in the total number. On his forty dogs Homén found a decrease in the ventral root fibers within the spinal cord. There was also a slightly larger proportion of small fibers on the operated than on the normal side. That some fibers degenerate and disappear from the ventral roots after the section of the mixed nerves has also been demonstrated by the Marchi reaction in animal experiments (Darkschewitsch '96, Redlick '93, Moschaew '93, Cassirer '98, Ceni '99, van Gehuchten '03).

The dorsal roots have undergone changes very similar to those in the ventral roots; the authors usually describe them together and in identical terms, so that the account just given of the latter would, with the following exceptions, serve equally well for the former. Dickinson ('68), and Friedländer and Krause ('86) found a considerable diminution in the number of dorsal root fibers although in both cases the ventral roots were reported practically normal. Marinesco ('92) also found more advanced atrophy, and Darkschewitsch ('96) more degenerating fibers in the dorsal than in the ventral root. The roots of the spinal nerves are subject to considerable normal variation in size, so that a large root might suffer considerable atrophy and still appear normal; and this is, no doubt, in large part responsible for the conflicting statements to be found in the literature.

It is obvious from the foregoing account that the roots show less pronounced alterations than the central portions of the severed nerve trunks. Friedländer and Krause's ('86) statement of this relation is worth some attention. We have already described

the atrophic nerve fibers which these authors saw in the central stumps and noted that they considered the ventral roots normal, and the dorsal roots altered only to the extent of the loss of a small portion of the fibers. The altered elements seen in the nerve were to be found neither in the ventral nor dorsal roots. But within the ganglia and especially at their distal extremities before the afferent fibers have mixed with those of the ventral roots the changes are seen at their maximum; hence the atrophy seen in the nerve stumps affects chiefly the peripheral branches of the T-processes. This has recently been confirmed by KLEIST ('04).

Asymmetry of the spinal cord due to atrophy of the corresponding halves of the segments associated with the injured nerves is an almost constant finding (not present in the cases reported by TÜRCK '53 and FRIEDREICH '73), and is due to changes in both the gray and the white substance. The only change in the white substance which occurs with sufficient regularity to be of significance is found in the dorsal funiculus; atrophy of the ventral and lateral funiculi have been occasionally reported. (Atrophy of the ventral funiculus, VULPIAN '69 and KAHLER and PICK '80; of the lateral funiculus, SWITALSKI '01; atrophy uniform over the entire half of the area of the white substance, LEYDEN '76, DÉJERINE and MAYOR '78.) That some loss of substance should occur in these fiber tracts is a necessary corollary of the cell destruction which, as we shall see, occurs in the ventral and dorsal cornua and in CLARKE's column; but this could lead to only a very slight atrophy. It is more probable that these few observations depend upon a natural asymmetry of the cord or a too superficial examination of the material. FRIEDLÄNDER and KRAUSE ('86) state that in many of their preparations it seemed as if the entire half of the cross-section were atrophied, but closer study showed that the loss was confined to the gray matter and the dorsal funiculus.

As is to be expected from its anatomical relations with the atrophied dorsal roots, the dorsal funiculus shows a decrease in the area of its cross-section which can be followed cephalad far beyond the segments primarily affected. In only four of the autopsy cases was it reported normal (VULPIAN '69, three cases; FRIEDREICH '73, one case). In some instances it was found reduced to two-thirds its original dimensions. To explain this, HOMÉN ('90) asserts that the individual fibers are smaller on the operated side;

but on the other hand FRIEDLÄNDER and KRAUSE ('86) state that they are normal and that the atrophy must be due to a decrease in their number. There can be no doubt that some disappear since the MARCHI stain reveals a certain number in the stages of disintegration (human material, FLATAU, '97; animal material, MOSCHAEW '93, CASSIRER '98, CENI '99). The degeneration does not appear to affect more than a small part of the fibers of the funiculus.

In all the cases of amputation reported since 1875 there is essential uniformity as regards the changes in the ventral cornu on the side of the amputation in the segments associated with the injured nerves. The area of the cross-section of the cornu as a whole is considerably decreased, sometimes by as much as one-third its normal dimensions. The number of motor cells has been determined in a number of cases and found below that of the normal side. It is especially the dorsolateral group of cells that is most affected; here there may be no more than two-thirds the original number (MARINESCO '92). The remaining cells are often shrunken, and devoid of processes.

In none of the amputation cases of the last thirty years has the dorsal cornu of the operated side been reported normal. The decrease in the area of the cross-section, which may amount to one-half the original area (SWITALSKI '01, case 4), is due in large part to the loss of medullated fibers (KNOPE '01). The substantia gelatinosa and the column of CLARKE are also markedly atrophied. The decrease in the size of the column of CLARKE is due to a loss of both fibers and cells, and is found in the segments some distance removed from those primarily affected (FRIEDLÄNDER and KRAUSE '86, HOMÉN '90, and others).

By far the most interesting point for us is the lack of data on the spinal ganglia; most observers have failed to take any note of them at all, or have overlooked the essential changes. REYNOLDS ('87) found an increased amount of connective tissue. MARINESCO ('92) states that although many nerve fibers had disappeared the spinal ganglion cells were intact. That these are the only instances where the spinal ganglia were studied in the autopsy cases is due, no doubt, to the difficulty of securing these structures in the hurry of the autopsy room.

HOMÉN ('90), in his extensive series of animal experiments, gave special attention to this subject, but failed to find any change except

an atrophy of the ganglion as a whole and of the nerve fibers contained in it. There seemed to be some atrophy of the ganglion cells but of this HOMÉN could not be sure. He did not consider the possibility of a decrease in the number of cells. CASSIRER ('98) states that a few cells in all probability undergo complete destruction. He says that the question of the loss of spinal ganglion cells can only be settled by resorting to an enumeration. Thus we see that in only four of the investigations were the spinal ganglia studied and even in these cases no important observations were made.

Some additional data have been furnished by various investigations based on NISSL's axonal reaction. After cutting the sciatic nerve near its exit from the pelvis in a number of dogs, LUGARO ('96), found that not all the cells of the spinal ganglion showed an equal degree of chromatolysis, a fact which he attributed to variations in the resistance of the individual cells. Thirty-nine days after the operation, there was a manifest diminution in the number of cells and an abundant proliferation of connective tissue. FLEMING ('97), who performed a similar operation on dogs and rabbits, found a decrease in size of the spinal ganglion cells soon after the operation. Cell destruction is, however, slow in making its appearance; in only one case is "disintegration of the protoplasm" noted at six weeks; after 18 weeks, however, many cells have disappeared. VAN GEHUCHTEN ('97), after cutting the vagus in rabbits, observed that the majority of the nerve cells in the ganglion nodosum underwent complete degeneration and disappeared. He believes that these results may be considered typical for the spinal as well as for the cerebral ganglia. On the other hand, MARINESCO ('98), after a similar operation on the vagus of dogs, found that the cells in the ganglion nodosum passed through the phase of reaction to a phase of restoration, and, therefore, did not undergo complete degeneration. In a rabbit six months after the operation he could not find the cell destruction of which VAN GEHUCHTEN speaks. MARINESCO also regards the reaction of the vagus as typical for all the cerebro-spinal ganglia. VAN GEHUCHTEN's observation has recently received support from the observations of KOSAKA and YOGITA ('05), who found, fourteen days after the section of the vagus in a young dog, an almost complete disappearance of the cells of the ganglion nodosum; of the thousands of cells only sixty-five remained.

KÖSTER ('03), having cut the sciatic immediately after its exit from the vertebral canal in cats, dogs and rabbits, found that all the spinal ganglion cells presented alterations of their tigroid bodies. Only a part of these cells suffered complete degeneration and this occurred for the most part after the 284th day. The phase of repair followed the chromatolysis in a large part of the cells and it was particularly in the large cells that the restoration of the tigroid substance was most evident. The cells that survived had undergone considerable atrophy. KLEIST ('04) made his experiments on half-grown cats and rabbits, cutting some of the upper cervical or lower thoracic nerves. After from three to six months a large proportion of the spinal ganglion cells (estimated at 33 per cent.) had disintegrated and the remaining cells had undergone a marked atrophy.

The practical bearing of this problem has been indicated by SCHÄFFER in his Text-book of Physiology: "If the observation of VAN GEHUCHTEN upon the nerve cells of the vagal ganglion after section of their peripheral fibers is correct, and is a phenomenon of general occurrence, it is difficult to see how the sensory fibers regenerate. Restoration of function in such cases may, perhaps, often be explained by the ingrowth of sensory nerve fibers from adjacent areas of distribution."

2. *Observations on the Second Cervical Nerve of the White Rat.*

The unsatisfactory character of the data on the changes in the spinal ganglia, resulting from the section of the associated nerves, emphasizes the necessity of some further investigation along this line, and in the experiments now to be described special attention was given to determining the extent of cell destruction in the ganglion. It is necessary, by way of preface, to state a few of the essential points concerning the relation of the spinal ganglion to the afferent fibers of the nerve and dorsal root. We may safely accept as the essential element, the unipolar cell with its T-shaped fiber, despite the fact that NISSL ('03) has called attention to some facts that point to another view. Nevertheless there are many cells in the ganglion which are not connected with medullated fibers in either the nerve or dorsal root, since enumerations show that the number of nerve cells in the ganglion far exceeds that of the medullated fibers in the root (HATAI '02), and by nearly as large an amount the number of medullated afferent fibers in the peripheral

nerve (HARDESTY '05). HATAI, working on the white rat, obtained the following results for the adult specimen of 167 gms. body weight.

TABLE I.

Ratio of Spinal Ganglion Cells to Dorsal Root Fibers. (HATAI.)

NERVE.	NUMBER OF CELLS.	NUMBER OF FIBERS.	RATIO.
VI C.	12,200	4,227	1: 2.8*
IV T	7,406	1,522	1: 4.8*
II L	9,442	1,644	1: 5.7

* The figures 2. 7 and 4. 3 given in the original are obviously misprints.

The writer in studying the normal relations in the second cervical nerve of the white rat has obtained results confirmatory of those of the authors already mentioned. In the three cases in which the dorsal root fibers and spinal ganglion cells were enumerated in the same individual nerve, a rather constant ratio of approximately 1 fiber to 3.2 cells was obtained. The first two specimens were seventy-two days old and weighed about 110 gms., the third was six months old and weighed 188 gms.

TABLE II.

Ratio of Spinal Ganglion Cells to Dorsal Root Fibers in the Second Cervical Nerve of the White Rat.

SPECIMEN.	NUMBER OF CELLS.	NUMBER OF FIBERS.	CELLS PER FIBER.
72 days old	7,721	2,472	3.1
72 days old	8,116	2,394	3.3
6 months old . . .	8,624	2,689	3.2

These results are corroborative of those obtained by earlier observers. The number of cells in a given spinal ganglion is about three times greater than the number of medullated fibers in the corresponding root. Without going into a discussion of the significance of this relation, it may be said that it is the large cells of the ganglion which alone are associated with medullated fibers (DOGIEL '96, HATAI '02). According to this view, 70 per cent. of the cells in the second cervical spinal ganglion of the white rat are small cells not associated with any medullated fibers which would be cut in dividing the peripheral nerve. It is obvious that these facts must have an important bearing on the results of injury to the nerve.

It is also important to note that the number of medullated dorsal root fibers is constantly increasing in the growing animal (HATAI '02). In the second cervical root of the white rat at twelve days of age the number of medullated fibers is less than that given in Table II, which represents the number in rats seventy-two days old. In two rats twelve days old the number of medullated dorsal root fibers was found to be 1608 and 1521, respectively. Hence, when the nerve is cut in animals of this age, even fewer medullated fibers are injured than would be the case in the adult animal.

It should also be mentioned that the number of dorsal root fibers may be taken as a fair indication of the number of afferent fibers in the peripheral nerve, the "distal excess" (HARDESTY '05) not being very large in this nerve of the rat. Table III shows that the ventral and dorsal rami of the nerve contain only 8 per cent. or 10 per cent. more fibers than are found in the ventral and dorsal roots. It is, therefore, not misleading to use the number of dorsal root fibers as an index of the afferent fibers in the peripheral nerve.

TABLE III.

Showing the Distal Excess in the II C. Nerve of the Adult White Rat.

Weight.	Ventral Root.	Dorsal Root.	Sum of Roots.	Distal Excess.	Percentage of D. E.	Sum of Rami.	Ventral Ramus.	Dorsal Ramus.
302 gms.	646	2,386	3,032	257	8	3,289	887	2,402
161 gms.	672	2,090	2,762	276	10	3,098	708	2,390

The present studies were carried out on white rats in which the second cervical nerve of the right side had been divided. Some animals, operated on when twelve days old, were allowed to live for two months, others for four months; the nerve was also cut in adult rats which were allowed to survive the operation four months. A numerical analysis was then made of the spinal ganglion and of the ventral and dorsal roots of the injured nerves, in order to determine to what extent degenerative changes had taken place and what amount of repair, if any, had occurred.

Technique.—In operating upon white rats twelve days of age it is necessary to work rapidly and to conserve, as far as possible, the body temperature. The little rat was held in position in the hands of an assistant with its neck slightly stretched and head bent forward. An incision was made in the midline on the back of the neck, with the atlas at its middle point, and carried down-

ward through the ligamentum nuchæ until the tuberculum posterius of the atlas was uncovered. The integument and long muscles of the neck were held aside by a spring retractor inserted through the median incision. The caudal margin of the atlas then served as a guide to the point where the right second cervical nerve emerges from the vertebral canal. A short stretch of the nerve[1] was laid bare and cut with sharp scissors about 1 mm. from the ganglion. No part of the nerve was resected and its central and peripheral ends were held in close proximity by the mass of tissue in which they were imbedded.

All blunt dissection was avoided; sharp instruments were used throughout, so that the tissues suffered a minimum amount of injury. It was not practicable to close the wound with deep sutures in the rats twelve days old, but this was done when the operation was performed on adult rats. The skin incision was closed with a collodion dressing.

Were it not for the fact that a standard objection to results obtained in this way is that they are due to a septic infection, the reader might be spared the usual paragraph on asepsis. Under the circumstances, however, some details must be given. The skin of the animal's neck, after it had been freed from hair, was thoroughly cleaned with ether-alcohol to remove oily deposits

[1]Only the dorsal division of the nerve was cut; the ventral division, which is much smaller, was not injured. This turns abruptly ventralward just distal to the spinal ganglion and was quite out of the field of the operation. In order to form some idea of what proportion of the afferent fibers were severed in cutting the dorsal ramus it is necessary to know the relative size of the two branches. In two cases studied, the proportion of fibers was as follows:

Specimen.	*Dorsal Ramus.*	*Ventral Ramus.*	*Ratio.*
9 months, 302 gms.	2,402	887	1:2.7
4 months, 161 gms.	2,390	708	1:3.3

The dorsal division is thus seen to be much the larger. It is mainly sensory since it forms the N. occipitalis major, which, after giving off a few muscular twigs, goes to the skin on the back of the head. The ventral division goes, in large part, to the muscles about its origin, only a small twig going to join the common trunk of the N. auricularis magnus and N. cutaneus colli which, in the rat, is formed chiefly by the ventral division of the third nerve.

From these data we may roughly estimate that about 13 per cent. of the afferent fibers of the second nerve go by way of the ventral branch and were not affected by the operation. This figure is obtained by regarding the ventral branch as a purely muscular nerve, which according to SHERRINGTON's ('94) observations should be composed of afferent and efferent fibers in the ratio of 2 to 3. This would give about 350 afferent fibers in the ventral branch, which, allowing for a 10 per cent. distal excess, would leave 315 represented in the dorsal root. The average number of dorsal root fibers in these two nerves was 2238, of which the 315 going to the ventral branch would constitute about 13 per cent.

and was then washed with a solution of mercuric chloride and left covered with a pad moistened in that solution, while the operator cleansed his hands. From this point on, the operator's hands touched nothing but the sterile instruments laid out on a sterile tray; all other things were handled by an assistant. Nothing touched the wound but the sterile instruments and sponges; the wound was too small to permit of introducing the fingers for any purpose.

Thanks to the natural resistance of the animals, as well as to the care taken to preserve the vigor of the tissues by the use of sharp instruments and hot sponges, the aseptic precautions were efficient, and not in a single case was there any sign of infection. (In one animal the collodion dressing came off after four days, but this one was at once discarded.) As final evidence that sepsis has nothing whatever to do with the results of these experiments, it may be said that in a series of animals killed five, six, seven, eight, twelve, seventeen and twenty days after the operation, the wound was found in perfect condition; and a microscopical study of the ganglion and nerve stump stained with toluidin-blue failed to show any indications of infection.

At the autopsy, note was made of the size of the neuroma and of any regeneration that had occurred. The operated nerve was then carefully dissected out together with its neuroma, ganglion, and roots, straightened out on a piece of card-board, and fixed in 1 per cent. osmic acid. The left, or normal nerves, were treated in the same manner as the right; but they were not used in the determination of the norm, since it was theoretically possible that their condition might in some way be influenced by the injury inflicted on the nerve of the opposite side. And, as a matter of fact, such a crossed degeneration has been reported in the ventral root fibers (Braeunig '03). For this reason it was considered safer to take the control material from entirely normal animals.

After fixation in 1 per cent. osmic acid, the tissue was imbedded in paraffin and cut into transverse sections. The sections of the roots were 3 μ to 4 μ thick; those of the ganglion were 12 μ thick and arranged in serial order. When a perfect series through the ganglion was not obtained the specimen was discarded.

The osmic acid not only stains the myelin of the nerve fibers, but also brings out the nerve cells so well that no further treatment is necessary. The technique of counting nerve fibers and spinal

ganglion cells has been described in a number of papers from this laboratory, and especially in the publications of HARDESTY. In counting fibers the net method was used. The entire ventral root and each of the fasciculi of the dorsal root and mixed nerve were, with few exceptions, small enough to come within one field of the microscope. The field was divided into small squares by a net micrometer placed in the ocular. The fibers in each square were counted in the order of the squares until the enumeration of the entire root or fasciculus was completed. The counting was done automatically by pressing the lever of a counting machine once for each fiber and reading off the final number from the face of instrument. In the few cases in which it was necessary to shift the preparation during the enumeration of a root or fasciculus, a straight line joining two prominent points was regarded as the limit between the two fields, and the position of this line was indicated by a line of the micrometer made to lie across the two points.

The enumeration of the nerve cells in the serial sections of the spinal ganglia was somewhat more difficult, since several successive sections may contain parts of the same cell. The difficulty was avoided by counting in a given section only those cells which showed nucleoli. These structures are small enough to escape division by the knife and so to lie, in the vast majority of the cases, within the plane of a single section. In most cases each cell has but one nucleolus, in rare instances there are two; but the presence of a pair would lead to error only in those extremely rare instances when the knife passed between them in such a way as to give a nucleolus to each of two sections of the same cell. HARDESTY estimates that this would not give an error of more than 0.2 per cent. The cells with nucleoli were enumerated with the aid of the counting machine in each section of the series; the sum of the numbers for the individual sections gave the total for the ganglion. Since a section of the ganglion could not all be brought into the field at once, it was necessary to use a mechanical stage which permitted a ready shifting of the preparation. In the spinal ganglion the different portions of the section are so characteristic that one does much better to dispense with the net micrometer and depend entirely upon the natural markings, which are adequate to prevent confusion as to what part of the section has been counted.

Results.—The results of the present investigation may all be summarized in the following table:

TABLE IV.

Showing the Numerical Relations of the II C. Nerve of the White Rat in the Normal Condition and after Section of the Ramus Posterior just Distal to the Ganglion.

Specimens.	Body Weight in gms.	Ganglion Cells.	Ventral Root Fibers.	Dorsal Root Fibers.	Neuroma	Regeneration.
Normal Rats.						
(1) 72 days old (normal)	110*	7,721	689	2,472	—	—
(2) 72 days old (normal)	110*	8,116	660	2,394	—	—
(3) 72 days old (normal)	155	9,343	—	—	—	—
(4) 72 days old (normal)	110*	—	590	1,959	—	—
(5) 72 days old (normal)	110*	—	591	2,217	—	—
(6) 240 days old, left (normal)	188	8,624	703	2,689	—	—
(7) 240 days old, right (normal)	188	—	773	2,891	—	—
Rats Operated on at 12 Days of Age and Killed after 60 Days.						
(8) 72 days old (operated)	110	3,845	523	2,641	large	partial
(9) 72 days old (operated)	110*	3,896	—	—	large	none
(10) 72 days old (operated)	110*	3,764	537	1,236	very small	none
(11) 72 days old (operated)	110*	4,193	506	1,983	medium	partial
(12) 72 days old (operated)	110*	4,497	431	1,607	large	partial
Rats Operated on at 12 Days of Age and Killed after 120 Days.						
(13) 132 days old (operated)	274	4,020	515	1,455	large	partial
(14) 132 day sold (operated)	146	4,516	646	2,357	very small	quite perfect
(15) 132 days old (operated)	161	—	562	1,987	small	partial
Rats Operated on at 140 Days of Age and Killed 120 Days Later.						
(16) 260 days old (operated)	225	4,215	610	1,983	large	none
(17) 260 days old (operated)	302	—	630	2,176	small	very slight
(18) 260 days old (operated)	264	4,176	506	2,219	large	none

The weights marked with a star (*) have been calculated from the age, no record having been taken of the body weight in these cases.

I. *Changes Produced by Section of the Nerve in Young Rats.*

The most interesting of the observations to be recorded in this place concerns the pronounced cell destruction that occurred in

the spinal ganglion; the extent and constancy of the degeneration is expressed in Table V.

TABLE V.

Showing the Decrease in the Number of Cells in the Spinal Ganglion Sixty Days After the Division of the Ramus Posterior of the II C. Nerve in Rats Twelve Days Old.

Normal.	*Operated.*
7,721	3,845
8,116	3,896
9,343	3,764
8,624	4,193
	4,497
4)33,804	5)20,195
Average.....8,451	4,039

Average loss 4,412

Per cent. average loss..... 52

From Table V we see that two months after the second cervical nerve had been cut in a rat twelve days old the corresponding spinal ganglion had lost about one-half its cells, and that this occurred with striking uniformity in five different specimens. Indeed, we find that the smallest number of cells in the operated ganglia, 3764, differs from the largest number 4497 by only 19 per cent. of the smaller number, while in the normal ganglia the greatest variation amounts to 21 per cent. Hence there can be little doubt but that the numerical differences which the operated ganglia show among themselves are due to normal individual variation present in the ganglia before the operation. We repeat, therefore, that this table shows an altogether striking uniformity in the number of cells in the operated ganglia, and that the number of cells dropping out of a ganglion must represent a certain constant percentage of the cells it originally contained. There must be some very definite reason for this constant reaction; but our knowledge of the architecture of the spinal ganglion is at present so vague that it is not possible to say what are the responsible factors.

If it is desired to know the percentage of cells that disappear, this may be determined by taking the average normal number of cells, 8451, as the base number, of which 4412, the average number of cells destroyed, constitutes 52 per cent. Here again we are totally at a loss for an explanation. We know of no anatomical relations which would justify the expectation of such a result.

The number of medullated afferent nerve fibers cut in the operation on a twelve-day old rat is about 1500. [The average number of medullated fibers in the dorsal roots of twelve-day old rats was found to be 1568 (p. 274); to this must be added a 10 per cent. "distal excess" to find the number of medullated afferent fibers in the nerve (p. 274); and from this result 13 per cent. must be subtracted for the afferent fibers running in the uninjured ramus anterior (p. 275). This calculation gives 1500 medullated afferent fibers which would be injured at the operation.] And were all the cells associated with these 1500 fibers to drop out, the loss would only amount to 17 per cent. Or, expressed in other words, nearly three times as many cells have disappeared as can be accounted for in terms of medullated axons injured at the time of the operation. Even if we assume that all the axons ever to develop are present (partly as non-medullated fibers) at the time of the operation on the young rat, and if we let this be represented by the number of medullated afferent axons in the adult nerve, we find that even this number, which does not exceed 2500 (see p. 274) is inadequate to account for the number of degenerated cells. For the explanation of these results we are, therefore, forced to fall back upon the existence of some as yet unknown relations within the spinal ganglion.

There was not sufficient disturbance of the blood supply to account for the degeneration, since the artery and vein accompanying each root were not in any way injured. The objection that the degeneration was due to a septic infection has been answered in connection with the discussion of the technique, and against such an objection there also speaks the fact that infection could not produce such uniform results.

It might be supposed that the fact that only the dorsal branch was cut and the ventral branch left intact explained the occurrence of a partial degeneration, and that if both branches had been cut all the cells would have disappeared. This supposition is, however, manifestly incorrect since the intact ventral branch did not contain more than 13 per cent. of the afferent fibers (see footnote, p. 275), and hence cannot be responsible for the 48 per cent. of the cells which survive.

The results obtained by the enumeration of the medullated nerve fibers in the ventral and dorsal roots of young rats surviving two months after the section of the second cervical nerve are much less

constant. The percentage of loss is much smaller than in the case of the ganglion cells, scarcely greater than the percentage of individual variation, so that the latter tends to render the former less evident. But this consideration only in part explains the lack of uniformity in the results; it seems that the degenerative processes in the root fibers are more variable than those in the ganglion cells and more directly dependent upon such conditions as reunion of the central and peripheral stump of the nerve.

TABLE VI.

Showing the Decrease in the Number of the Medullated Nerve Fibers in the Ventral and Dorsal Roots Two Months After the Section of the Ramus Posterior of the II C. Nerve in Rats Twelve Days Old.
(Normal and "Operated" Material from Different Animals.)

	Ventral Root.		Dorsal Root.	
	Normal.	Operated.	Normal.	Operated.
	689	523	2,472	2,641
	660	537	2,394	1,236
	590	506	1,959	1,983
	591	431	2,217	1,607
Sum.....	2,530	1,997	9,042	7,467
Average.....	632.5	499.2	2,260.5	1,866.7
Average loss.....	133.3		393.8	
Average (%) loss.....	21		17	

The ventral roots show a fairly uniform loss of fibers. The smallest number of fibers in the normal roots (590) exceeds by 53 the largest number in the operated roots (537). Moreover, the average of the operated roots falls 133 behind the average for the normal roots, making an average loss of 21 per cent. This loss is, however, by no means so uniform as that in the number of spinal ganglion cells. The loss of fibers in the ventral root is in harmony with the results reported by numerous investigators who found, as a result of cutting the peripheral nerve, fibers present in the ventral root which gave the MARCHI reaction (p. 268). It is also a necessary result of the degeneration of the cells of the ventral cornu of the spinal cord so constantly found after the section of nerves (p. 270).

Even more variability is shown in the column of Table VI representing the operated dorsal roots. The first operated dorsal root that was subjected to an enumeration contained 2641 nerve fibers,

a number even greater than the normal average for rats of that age. The other three roots fall below the normal; in one case the number goes as low as 1236. The average loss is 393 fibers or 17 per cent.

The deficiency of fibers in the dorsal roots, associated with the injured nerves, finds its counterpart in the degenerating fibers which may be recognized by the method of MARCHI (see p. 267). According to recorded observations the degenerating fibers constitute only a fraction of the total number. To what extent degeneration occurred in our specimens can only be determined by study of the roots with the MARCHI method, because it is not possible to say what part of the fibers, enumerated in this investigation have been formed since the operation as an attempt to repair the damaged root.

TABLE VII.

Showing the Relation of the Number of Dorsal Root Fibers to Spinal Ganglion Cells in the Operated II C. Nerve of the White Rat.

SPECIMEN.	SPINAL GANGLION CELLS.	DORSAL ROOT FIBERS.	RATIO.
Rat 8.....	3,845	2,641	1:1.4
Rat 10.....	3,764	1,236	1:3.0
Rat 11.....	4,193	1,983	1:2.1
Rat 12.....	4,497	1,607	1:2.7
Average of 3 normal rats (Table II)	8,153	2,485	1:3.2

Table VII shows that in every case there are more than enough spinal ganglion cells to account for the dorsal root fibers, although in one case the excess of cells is not very great. By comparison with the average normal ratio taken from Table II, it will be seen that the ratio of cells to fibers is reduced in the operated nerves, and that while in the normal nerve it is approximately constant at one fiber to 3.2 cells in the operated nerves it shows much greater variation. The table also shows that there is no constant relation between the number of spinal ganglion cells destroyed by the operation and the number of dorsal root fibers which are found two months later; and that, therefore, the loss of dorsal root fibers cannot, without some qualification, be attributed to the degener-

ation in the spinal ganglion. The possible factors which may complicate the result are given in the footnote, on p. 275.

II. *The Influence of the Length of the Post-operative Period upon the Results.*

After the changes just described had been found in the rats that had survived the operation for two months, the question arose whether the degeneration had come to an end before the animal was killed, and whether if the rat were allowed to live for a longer period of time, further changes might not take place. It was thought possible that the number of spinal ganglion cells might further decrease, and that the roots might either continue to lose fibers, or perhaps show a tendency to repair.

TABLE VIII.

Showing the Numerical Relations in the II C. Nerve in Rats which Lived Four Months after Section of the Ramus Posterior of that Nerve when the Animals were Twelve Days Old.

	Spinal Ganglion Cells.	Ventral Root Fibers.	Dorsal Root Fibers.
	4,020	515	1,455
	4,516	646	2,357
		562	1,987
Average	4,268	574	1,933

TABLE IX.

Showing the Influence of the Lapse of Time upon the Effect of Cutting the II C. Nerve.[1]

Average Number of	2 Months After the Operation.	4 Months After the Operation.
Ganglion Cells	(5) 4,039	(2) 4,268
Ventral Root Fibers	(4) 499	(3) 574
Dorsal Root Fibers	(4) 1,866	(3) 1,933

[1]The figures in parentheses indicate the number of cases from which the averages were obtained.

From Table IX we see that the number of spinal ganglion cells, although still far below the normal, is a little greater in the specimens removed after four months than in those removed after two

months. According to our present knowledge there is no reason to expect any regeneration of the spinal ganglion cells. This statement is based in part on HATAI's ('02) study of the growth changes in the spinal ganglia, but more particularly on the negative results of a series of investigations undertaken for the purpose of testing the regenerative capacity at one time supposed to belong to these structures (TIRELLI '95, MONTI and FIESCHI '95). The slight excess of cells in the four-month specimens is probably of no significance, representing nothing more than the individual variation of which so much has already been said. Further support is given to this view by the fact that of the two specimens enumerated the first gives a figure close to the average for the two-month specimens while the second runs much higher and in all probabilty represents a large ganglion which originally contained over 9000 cells.

The point of importance is not that there is a slight excess of cells in the four-month specimens, but that there is certainly no decrease, and that, therefore, the process of cell-destruction runs a rather rapid course and is completed during the first two months, after which there is no further change. This is of interest in connection with the usual doctrine that in chromatolysis the phase of reaction is followed by a phase of restitution, which may result in the complete restoration of the cell, or may in turn give place to a phase of degeneration, resulting in the gradual disappearance of the injured neurones. It is obvious that in this case the phase of degeneration (if it can properly be separated as a distinct phase at all) must have been a rapid one which came to a definite termination. It did not result in the destruction of cell after cell until all had disappeared. According to recent observations of KÖSTER ('03), who cut the sciatic nerve in cats, rabbits and dogs, the cell destruction in the spinal ganglia is only slightly noticeable after 100 days, but is very marked after 284 days. There can be no doubt that in my experiments on rats the degeneration was complete before the end of the first sixty days. That my animals were very young and of a different zoölogical order from those of KÖSTER, may in part explain the discrepancy in the results. It should be mentioned, however, that KÖSTER did not control his observations by an actual enumeration of the cells.

By reference to Table IX it will be seen further that the number of ventral root fibers is greater in the animals which survived four months than in those which were killed at an earlier date. The

difference, howeve amounts to only 15 per cent. of the smaller number, and this can readily be accounted for in terms of normal growth. There seems, therefore, to be little if any tendency to repair the ventral roots in the sense of an acceleration of the normal rate of fiber formation to compensate for a previous loss. Of course the neurones represented by the degenerating fibers in the root undergo complete destruction (p. 270) and no regeneration of the injured axons could be expected. But it was deemed possible that some reserve cells might be located in the ventral cornua, which might take part in a reformation of the ventral root after the neurones whose axons originally entered into its formation had been destroyed. There is no evidence that such a compensatory process occurred in this set of experiments; and if reserve cells are present in the ventral cornua of the spinal cord, they certainly failed to respond to the demands placed upon them by the conditions of this experiment.

The excess of fibers in the dorsal roots four months after the operation, as compared with those at the two-month period, amounts to less than 1 per cent. This is less than would be expected on the basis of normal growth processes, and it is certain that during the second two of the four months intervening between the operation and the autopsy there was no tendency for the small latent cells to increase their normal rate of development in an attempt to restore the atrophied dorsal roots to their normal condition.

The fact that both the ventral and dorsal roots show more fibers four months after the operation than at an earlier period, indicates very clearly that there can be no slow progressive degeneration going on in these localities. This fact is of interest, since retrograde degeneration has usually been regarded as a chronic progressive process. In this case it ran a rather rapid course and came to a definite termination.

III. *Significance of Differences in the Ages of the Animals.*

It has been shown what the effects of cutting the second cervical nerve are in the young rat and what influence is exerted by the lapse of a greater or less length of time between the operation and the autopsy. It is now our purpose to inquire how far these results are dependent upon the immaturity of the animal used for

the experiment. It was anticipated that the section of the nerve would not be nearly as destructive of spinal ganglion cells in the adult, as it had been in the younger animals; and the results expressed in Table X came as something of a surprise to the writer.

TABLE X.

Showing the Effect of Cutting the II C. Nerve in Adult Rats (140 Days Old) which Survived 120 Days.

	Spinal Ganglion Cells.	Ventral Root Fibers.	Dorsal Root Fibers.
	4,215	610	1,983
	4,176	506	2,219
		630	2,176
Average	4,195	582	2,126

TABLE XI.

Showing the Influence of the Age of the Animal and the Length of the Post-operative Period upon the Effect of Cutting the II C. Nerve in the White Rat.[1]

Age at the operation.....	12 days	12 days	4 months
Period of survival.....	2 months	4 months	4 months
Spinal ganglion cells	(5) 4,039	(2) 4,268	(2) 4,195
Ventral root fibers	(4) 499	(3) 574	(3) 582
Dorsal root fibers	(4) 1,866	(3) 1,933	(3) 2,126

[1]The figures in parentheses indicate the number of cases from which the averages were obtained.

From Tables X and XI it will be apparent that there was found a slightly greater number of cells in the spinal ganglia of the animals operated on when already adult, than in the first set of young rats, but fewer than in the second set. It is believed that the difference is in each case merely a matter of individual variation in the original ganglia, and is, therefore, of no consequence. That the section of the nerve should entail practically the same effect upon the spinal ganglion, whether it is made in the young or in the adult animal, is a matter of a good deal of interest and a result quite contrary to precedent. It is the more difficult to understand because at least 30 per cent. more medullated afferent fibers were cut in the operation upon the adult than in that upon the young rat (p. 274), and it is hard to see how this should have been so exactly compensated for by a greater resistance of the adult neurones. There is a possibility that even in the rat twelve days old

all the peripheral fibers ever to develop are present in the nerve, some as medullated, the rest as non-medullated fibers; and this if it should be found to be the case, would help to explain the fact that the reaction is the same in the adult as in the young animals.

Table XI gives only the average number of cells present in the ganglia under each of the three conditions; Table XII shows that the agreement which was found between the averages is just as apparent when all the individual ganglia are brought together. It does not matter whether the animal is young or old or whether it survives for two or for four months; the changes in the spinal ganglion are always the same.

TABLE XII.

Showing the Uniformity in the Cell Destruction in the Spinal Ganglion Resulting from the Section of the Peripheral Nerve.

NORMAL.	OPERATED WHEN 12 DAYS OLD, LIVED 2 MONTHS.	OPERATED WHEN 12 DAYS OLD, LIVED 4 MONTHS.	OPERATED WHEN 140 DAYS OLD, LIVED 4 MONTHS.
—	3,845	—	—
8,116	3,896	—	—
7,721	3,764	—	—
8,624	4,193	4,020	4,215
9,343	4,497	4,516	4,176

By reference to Table XI it will be seen that the number of ventral root fibers is nearly the same in both sets of rats that survived four months, whether the operation was made when they were 12 or 120 days old. This indicates that the same number of ventral root fibers dropped out in each case, after which the nerve fibers continued to develop at the normal rate in the immature animal. Hence, since the number of medullated fibers was smaller in the young rat, those that degenerated must have constituted a larger proportion of the entire number than in the case of the adult rat. And this is in accord with the general belief that immature neurones succumb more readily to an axonal lesion than do the fully developed ones. This variation in reaction, according to the age of the animal, is very pronounced in the case of the fibers of the corpus callosum (RANSON '04). In a rat twelve hours old in which the corpus callosum was injured, the injured fibers underwent complete degeneration, both Wallerian and retrograde; in a rat of three months the retrograde degeneration affected only the part of the fiber in the immediate vicinity of the lesion.

The dorsal roots show distinctly more fibers in the animals operated on at four months of age than in either of the other cases (Table XI); since, as Table IV clearly indicates, these older animals do not possess as much regenerative capacity, and since it is certain that at least one-third more medullated fibers were cut in operating upon them, it seems altogether probable that the large number of fibers in the dorsal roots in the adult rats is to be explained as in the case of the ventral roots on the basis of a greater resistance of the adult neurones.[1]

The interpretation of the numerical results obtained for the spinal ganglion and dorsal root is exceedingly difficult. A final statement can only be made when we have the results of the MARCHI test and the NISSL stain to assist us in drawing conclusions, since in these ways we can tell what proportion of the fibers degenerate and whether the large or the small cells are chiefly concerned in the changes going on in the ganglion. Investigations along these lines are now in progress.

[1] At first sight it seems a contradiction to say that the dorsal roots show varying degrees of resistance, but that there is no difference in the degree of degeneration seen in the spinal ganglion. If, however, it were the small cells not directly associated with medullated fibers that had disappeared from the ganglion it would be easy to understand how the dorsal root fibers, associated as they are with the large cells, would be quite independent of the decrease in the number of the ganglion cells. These large cells with their medullated processes would then suffer varying degrees of injury, usually not resulting in the destruction of the perikarya, but in a certain proportion of the cases bringing about a degeneration of the associated dorsal root fibers. The more mature the animal, the less seriously would the large neurones be injured, and the fewer would those be that could not maintain their dorsal root fibers intact.

The possible causes of variation in the dorsal roots may be stated as follows:

1. While the total number of cells destroyed is constant, the proportion of large and small cells affected may vary, and accompanying a greater destruction of large cells, there may be a greater degeneration of the dorsal root. This supposition is very improbable.

2. All the large cells may drop out in every case, the variation in the dorsal roots depending upon the extent of the compensatory development of the small cells.

3. Most of the large cells may pass through the stages of reaction and repair, while the small cells drop out in large numbers. In this case the medullated nerve fibers associated with a varying number of large neurones might degenerate although the perikarya of these same neurones survive. This is the most probable explanation of the results, as will be shown in another paper. At the present moment it seems probable that the key to the explanation of all these conflicting results is to be found in the existence in the nerve of many non-medullated fibers which are the axons of the small cells. This would furnish an explanation for the degeneration of the small cells after the section of the nerve.

IV. *Effect of Reunion of the Cut Ends of the Divided Nerves.*

It is clear from Table IV that, so far as the survival of spinal ganglion cells is concerned, it is a matter of indifference whether regeneration of the nerve occurs or not. In four cases no regeneration occurred at all; in the other six cases the extent of the regeneration varied considerably; in one case (14) an almost perfect nerve was found, with only a slight thickening to indicate the point of division. But with this wide range in the degree of the restoration of the peripheral nerve, there is no difference in the condition of the spinal ganglion. This shows very clearly that the degeneration of spinal ganglion cells is not markedly influenced by the regeneration or lack of regeneration of the peripheral nerve. MARINESCO ('98) states that unless there is union of the divided ends of the nerve, the motor cells of the ventral cornua do not pass from the phase of reaction to the phase of restoration, but atrophy and disappear. The entrance upon the phase of restoration is, according to him, an indication that regeneration has begun in the nerve. VAN GEHUCHTEN ('99) and FOA ('99) have been unable to confirm these observations of MARINESCO for the motor nuclei, and my results would indicate that for the spinal ganglia the restoration of the cells is entirely independent of the restoration of the peripheral nerve.

CONCLUSIONS.

As a result of dividing a peripheral nerve, there occurs not only the typical Wallerian degeneration of the distal portion but also various changes in the proximal portion of the nerve, the spinal ganglion, the ventral and dorsal roots and the spinal cord. In all these regions there take place both a simple atrophy and a true degeneration. The atrophy results in a decrease in the size of the fibers, many of which entirely lose their medullary sheaths. Many of the cells of the ventral cornua and of the spinal ganglion are markedly atrophic. The degeneration in the fibers proximal to the lesion begins some weeks later than Wallerian degeneration, from which, however, it cannot be distinguished histologically. This retrograde degeneration affects only a part of the fibers and can be found not only in the central stump and the ventral and dorsal roots but also in the intramedullary continuations of the root fibers. This results in a distinct diminution of the number of nerve fibers

in these regions and helps to increase their atrophic appearance. The degeneration of nerve cells results in the disappearance of a certain, apparently variable, number of ventral horn cells and a very considerable and constant number of spinal ganglion cells.

It has been shown by careful enumeration that after cutting the second cervical nerve of the white rat, one-half of the cells in the corresponding spinal ganglion degenerate and disappear. This reaction is very constant and uniform; in the nine ganglia studied the percentage of variation is no greater than the percentage of individual variation in the normal ganglia. This is peculiar in that many more cells disappear than can be accounted for in terms of medullated fibers cut at the time of the operation; and while it is not possible at present to give a satisfactory explanation of the results they point to some as yet unknown relations in the ganglion.

The number of fibers in the dorsal root is open to much greater variation; but there is on the average a loss of about 17 per cent. The dorsal roots seem more susceptible to the degenerative changes in the young than in adult animals.

The degeneration of ganglion cells is constant, that of the dorsal root fibers is variable and is much less extensive than would be expected from the number of cells which disappear. This shows that the degeneration in the dorsal roots cannot without some qualification be attributed to the degeneration in the spinal ganglion. It is hoped that an investigation now in progress will supply the necessary data for the interpretation of these results.

Contrary to the usual conception, the degeneration of fibers and cells was not progressive; it had been completed before the end of the first two months, after which there was no further change.

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